REVIEW ARTICLE

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Psychotic Disorders

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The term "psychosis," which is derived from the Greek word for abnormal condition of the mind, has been used in many different ways in clinical medicine. Before 1980, the term "psychotic" was applied generically to persons whose mental functioning was sufficiently impaired to interfere with their capacity to meet the ordinary demands of life. Starting in 1980 with the publication of the third edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III), the term indicated gross impairment in reality testing — that is, disruption of the ability to distinguish between the internal experience of the mind and the external reality of the environment.

To achieve greater diagnostic precision, DSM-IV, published in 1994, defined psychosis more specifically to apply to mental disorders characterized by symptoms such as fixed false beliefs (delusions, such as the belief that one is being poisoned by neighbors who are piping gas through the walls), hallucinations, disorganized thoughts (illogical and incoherent speech, neologisms, and made-up words), clang associations (rhymed words), word salad (nonsensical sentences), echolalia (repetition of spoken words), and abnormal motor behavior (bizarre postures, stereotypy, and waxy flexibility).

The psychotic disorders in the current edition of the diagnostic manual, DSM-5, are defined by clinical syndromes rather than diseases and are distinguished from one another mainly by their duration (e.g., ≥6 months for symptoms of schizophrenia and <1 month for a brief psychotic disorder), by symptom profile (e.g., multiple types of psychotic symptoms in schizophrenia and only delusions in delusional disorder), by the relationship between psychotic symptoms and episodes of disturbed mood (i.e., whether the psychotic symptoms occur during, or extend beyond, a mood disturbance), and by cause (i.e., whether the psychotic symptoms are due to the use of such substances as phencyclidine [PCP] or to medical conditions that affect the brain, such as epilepsy, systemic lupus erythematosus [SLE] and other autoimmune diseases, tumors, or dementias). In the current clinical nomenclature, "psychotic symptom" denotes a manifestation of cognitive or perceptual dysfunction, mainly delusions or hallucinations, whereas "psychotic disorder" refers to a condition in which psychotic symptoms meet specific diagnostic criteria for a disease.

Psychoses can be categorized into three broad groups: idiopathic psychoses, psychoses due to medical conditions (including neurodegenerative disorders), and toxic psychoses (due to substances of abuse, prescribed medications, or toxins) (Table 1). Conditions for which the cause or pathological features of psychosis are known and can be treated by directly targeting the causal agent or its pathological consequences are classified separately from the idiopathic conditions. These classifications are arbitrary, reflecting the limitations of our knowledge about psychotic disorders, and are likely to change as scientific research reveals the pathological basis and causes of these disorders.

NATURAL HISTORY OF PSYCHOSIS

The age at which psychotic symptoms first appear and their temporal evolution vary according to the underlying disorder. The most common psychotic disorders, such as schizophrenia, bipolar disorder, and depression with psychotic symptoms, begin in the late second or third decade of life, whereas delusional disorders more often develop in middle age, and psychoses due to neurodegenerative diseases such as Alzheimer's disease begin during senescence. Psychotic symptoms caused by drug abuse or prescribed medications and symptoms caused by medical disorders such as SLE, seizures, or fevers can occur at any age. Features that suggest a secondary psychosis (i.e., toxic psychosis or psychosis due to medical conditions) rather than an idiopathic type include a rapid decline in functional capacity from premorbid levels; an abrupt onset of symptoms without clear precipitants; a history of headaches, seizures, or visual, olfactory, or tactile hallucinations; and an absence of a family history of psychotic disorders.

Idiopathic psychotic disorders, especially schizophrenia and schizoaffective disorder (the latter characterized by symptoms of schizophrenia and a mood disorder such as depression or mania), usually evolve through premorbid, prodromal, syndromal, progressive, and chronic stages (Fig. 1).[1] However, the course of illness is unpredictable, and the frequency, number, and types of psychotic symptoms vary according to the specific psychotic disorder and can differ from one patient to another with the same disorder (Table 1).

Persons with psychotic disorders are at risk for complications and derivative effects of psychosis, particularly suicide attempts (lifetime prevalence, 34.5%),[2] substance abuse (lifetime prevalence, 74%),[3] homelessness (annual prevalence, 5%),[4] victimization by others (prevalence over a 3-year period, 38%),[5] and committing acts of violence (increase in the odds of violence, as compared with the general population, 49 to 68%).[6]

CAUSES AND PATHOPHYSIOLOGICAL FEATURES

NEUROTRANSMITTERS IN PSYCHOSIS

As a consequence of their pathology, many disorders that have different causes and pathophysiological characteristics have altered neurotransmission in the dopamine and glutamate pathways of the hippocampus, midbrain, corpus striatum, and prefrontal cortex (Fig. 2), which leads to the emergence of psychotic symptoms. This pathophysiological model of psychosis is based on many studies that suggest that excess synaptic levels of dopamine and glutamate cause increased postsynaptic stimulation, the downstream effects of which result in psychotic symptoms.[7,8] The molecular bases of these disturbances include deficiency of γ-aminobutyric acid (GABA) inhibitory interneurons and hypofunctioning *N*-methyl-D-aspartate (NMDA) glutamate receptors (NMDARs), which alter the inhibitory–excitatory balance of neural systems mediated by glutamate and dopamine.[9,10] A recent study suggests that other molecular mechanisms that regulate glutamate synthesis or metabolism might also contribute to the dysregulation and increased synaptic level of glutamate.[11]

Studies of several types of induced psychosis have been informative in understanding these neurotransmitter mechanisms. For example, natural and synthetic cannabinoid formulations containing specific cannabis receptor–subtype agonists, particularly the cannabinoid-1 receptor agonist, can induce psychosis or increase the risk of its occurrence. Cannabinoid receptors act on molecular elements and guide the trafficking of dopamine and glutamate at neuronal synapses.[12,13] Other so-called designer drugs, such as "bath salts," a synthetic cathinone that potently releases dopamine and serotonin, induce fulminant psychotic symptoms in a similar fashion.

A specific type of psychosis is caused by stimulation of the main serotonin receptor subtype, 5-hydroxytryptamine subtype 2A (5-HT_{2A}). Psychedelic drugs, such as lysergic acid diethylamide (LSD), mescaline, and psilocybin, have mental effects that mimic psychotic symptoms primarily through what has been termed "biased" stimulation of 5-HT_{2A} receptors, meaning that these drugs selectively activate noncanonical intracellular signaling pathways.[14] Although this observation implicates serotonin and 5-HT_{2A} receptors in the pathophysiology of psychotic disorders, psychedelic drugs induce mental aberrations that are qualitatively different from idiopathic psychotic disorders and from those caused by psychostimulants such as ampheta-

Table 1. Clinical and Pathophysiological Features and Treatment of Disorders in Which Psychotic Symptoms Occur.*

Psychotic Disorder	Psychotic Symptoms	Distinguishing Features	Lifetime Prevalence (%)	Basis for Diagnosis	Pathophysiology	Treatment	Complications
Idiopathic primary psychoses							
Schizophrenia	Delusions, hallucinations (mostly auditory), disorganized thinking, disorganized or abnormal psychomotor behavior	Active-phase psychotic symptoms with prodromal and residual-phase symptoms, ≥6-mo duration, decline in functioning†	0.30–0.87	Clinical	Genetic factors, neurodevelopmental factors, dopamine, glutamate	APDs, psychosocial therapies	Substance abuse, suicide, agitation, victimization, violence
Schizoaffective disorder	Delusions, hallucinations (mostly auditory), disorganized thinking, disorganized or abnormal psychomotor behavior	Psychotic symptoms (delusions and hallucinations) and mood symptoms occurring concurrently or independently	0.32	Clinical	Genetic factors, neurodevelopmental factors, dopamine, glutamate	APDs, antidepressants, mood stabilizers, psychosocial therapies	Substance abuse, suicide, agitation, violence
Bipolar disorder with psychotic features	Delusions, hallucinations	Psychotic symptoms during manic episodes	0.12	Clinical	Genetic factors, neurodevelopmental factors, dopamine, glutamate	APDs, mood stabilizers, psychosocial therapies	Substance abuse, suicide, agitation, violence
Major depressive disorder with psychotic features	Delusions, hallucinations	Psychotic symptoms only during depressive episodes	0.33	Clinical	Genetic factors, dopamine, glutamate	APDs, antidepressants, ECT, psychosocial therapies	Substance abuse, suicide, agitation, violence
Delusional disorder	Delusions	Functioning not impaired apart from impact of delusions	0.18	Clinical	Genetic factors, dopamine, glutamate	APDs, CBT	Violence
Schizophreniform disorder	Delusions, hallucinations, disorganized thinking, disorganized or abnormal psychomotor behavior	Psychotic symptoms lasting 1–6 mo	0.07	Clinical	Genetic factors, neurodevelopmental factors, dopamine, glutamate	APDs, psychosocial therapies	Substance abuse, suicide, agitation, violence
Brief psychotic disorder	Delusions, hallucinations, disorganized thinking, disorganized or abnormal psychomotor behavior	Psychotic symptoms lasting <1 mo	0.05	Clinical	Dopamine	APDs, CBT	Substance abuse, suicide, agitation, violence
Postpartum psychosis	Delusions, hallucinations	Psychotic symptoms within 6 wk after delivery	0.07‡	Clinical	Hormonal factors, dopamine, glutamate	APDs	Substance abuse, suicide, agitation, violence

Toxic psychoses							
Psychosis induced by recreational substances§	Delusions, hallucinations	Psychotic symptoms temporally related to substance intoxication or withdrawal	0.42	Toxicologic assays for drugs	Dopamine, glutamate	Drug elimination	Suicide, agitation, violence
Psychosis induced by toxins¶	Delusions, hallucinations	Psychotic symptoms temporally associated with toxin exposure		Toxicologic assay	Dopamine, glutamine	Toxin elimination	Agitation
Iatrogenic psychosis‖	Delusions, hallucinations	Psychotic symptoms as a medication side effect		Temporal association with a medication known to cause psychotic symptoms	Dopamine, glutamine	Discontinuation of medication	Agitation
Psychoses due to medical conditions							
Neurologic, endocrine, metabolic, and other conditions**	Delusions, hallucinations	Psychotic symptoms temporally related to medical condition		Temporal association with a medical condition known to cause psychosis		APDs, treatment of underlying medical condition	Agitation, self-injury

* APD denotes antipsychotic drug, CBT cognitive behavioral therapy, and ECT electroconvulsive therapy.
† Active-phase symptoms include delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, and negative symptoms. A person must have at least two of these to be considered in the active phase of schizophrenia. Residual-phase symptoms include negative symptoms and accentuated versions of the active-phase symptoms (e.g., odd beliefs and unusual perceptual experiences).
‡ The 0.07% represents the incidence of hospitalization for postpartum psychosis.
§ Recreational substances include alcohol, cannabis and its derivatives, hallucinogens, phencyclidine and related substances, inhalants, sedatives, hypnotic agents, anxiolytic agents, and stimulants (including cocaine).
¶ Toxins include anticholinesterase, organophosphate insecticides, sarin and other nerve gases, carbon monoxide, carbon dioxide, and volatile substances such as fuel or paint.
‖ Iatrogenic psychosis is induced by anesthetics and analgesics, anticholinergic agents, anticonvulsants, antihistamines, antihypertensive and cardiovascular medications, antimicrobial medications, antiparkinsonian medications, chemotherapeutic agents (e.g., cyclosporine and procarbazine), glucocorticoids, gastrointestinal medications, muscle relaxants, nonsteroidal antiinflammatory drugs, other over-the-counter medications (e.g., phenylephrine and pseudoephedrine), antidepressant medications, and disulfiram.
** Neurologic conditions include neoplasms, cerebrovascular disease, Huntington's disease, multiple sclerosis, epilepsy, auditory- or visual-nerve impairment, deafness, migraine, and central nervous system (CNS) infections; endocrine conditions include thyroid, parathyroid, and adrenocortical abnormalities; metabolic conditions include hypoxia, hypercarbia, and hypoglycemia; and other conditions include fluid or electrolyte imbalances, hepatic or renal diseases, and autoimmune disorders with CNS involvement (e.g., systemic lupus erythematosus).

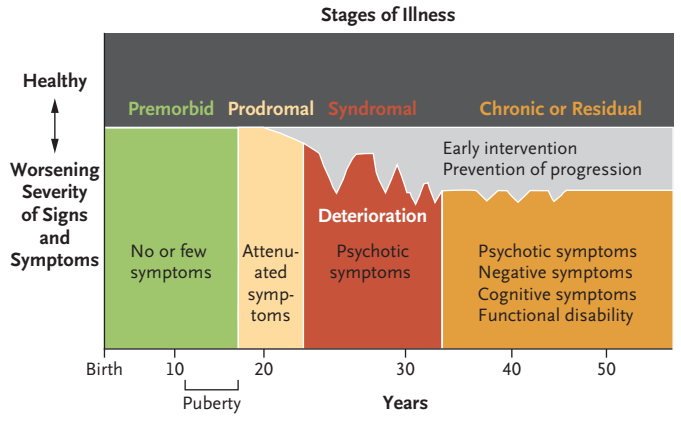

Figure 1. Natural History of Schizophrenia and the Rationale for Preventing Chronic Disease.

Shown are the stages of illness in schizophrenia, the prototypical idiopathic psychotic disorder. Detection and treatment in the early stages of illness, ideally close to the onset of the first episode of psychosis, shorten the duration of psychotic episodes, reduce recurrences, and limit the progressive decline in functioning (deterioration) that occurs in the syndromal stage and leads to the chronic effects of the disease. The syndromal stage begins with the first episode of psychosis and continues through the progressive stage.

mine and NMDA antagonists, which stimulate glutamate activity.[7,8,15]

GENETIC FACTORS IN PSYCHOSIS

Epidemiologic studies strongly implicate heredity in the pathogenesis of the idiopathic psychotic disorders. Schizophrenia and bipolar disorder with psychotic symptoms are characterized by approximately 50% concordance of certain genetic loci between identical twins, and among the siblings and parents of persons with an idiopathic psychotic disorder, rates of the same disorder are 10 to 15 times as high as the rates in the general population. Although the specific genetic markers and modes of heritance of psychotic disorders have not been determined, two general hypotheses have been proposed: the common disease–common allele hypothesis (genes with >10% population frequency) and the common disease–rare allele hypothesis.[16] According to the first hypothesis, prevalent genes with low penetrance act additively and through epistasis with other such genes to confer a risk of schizophrenia and psychotic mood disorders. The second hypothesis implicates rare inherited or de novo mutations, or copy-number variants, that occur only in a small proportion of cases (approximately 2.4%) but are highly penetrant.

Common Genetic Variants with Low Penetrance

Of the many genes that have been associated with a risk of psychotic disorders, only a few are biologically plausible. Several associations have been found between idiopathic psychosis and genes controlling synaptic neurotransmission, particularly genes involving pathways mediated by dopamine and glutamate.[17] These associations, which are consistent with current neurotransmitter theories of psychotic disorders, are reasonable but have not been proved to be valid. A provocative recent finding is an association between psychosis and genes involved in immunologic function, such as the major histocompatibility complex (MHC) locus and complement.[18] MHC molecules in the central nervous system regulate the development of neuronal connections through microglia-guided pruning of presynaptic terminals, thus influencing the formation of neural circuits and the functions that they mediate.[19,20]

Rare Genetic Variants with High Penetrance

The most common genetic abnormality associated with a psychotic disorder is the chromosome 22q11.2 microdeletion. This causes the 22q11.2 deletion syndrome (also known as the velocardiofacial syndrome or the DiGeorge syndrome), which occurs in approximately 1 in 4000 live births. This disease is associated with cardiac, facial, and limb abnormalities, and approximately 25% of affected patients have symptoms of schizophrenia or schizophrenia-like features that are largely indistinguishable from idiopathic schizophrenia.[21] Other copy-number variations have been described that vary with respect to population frequency and penetrance, as well as their association with psychotic disorders.[22]

NEURODEVELOPMENTAL FACTORS IN PSYCHOSIS

Exposure to prenatal environmental insults (e.g., maternal infections, drug toxicity, and nutritional deficiencies), birth complications, postnatal trauma, and other forms of deprivation at critical stages of development is associated with a risk of subsequent psychotic disorders. Although their effect sizes are small, these environmental factors are thought to interact with genetic factors and increase susceptibility to psychotic disorders,

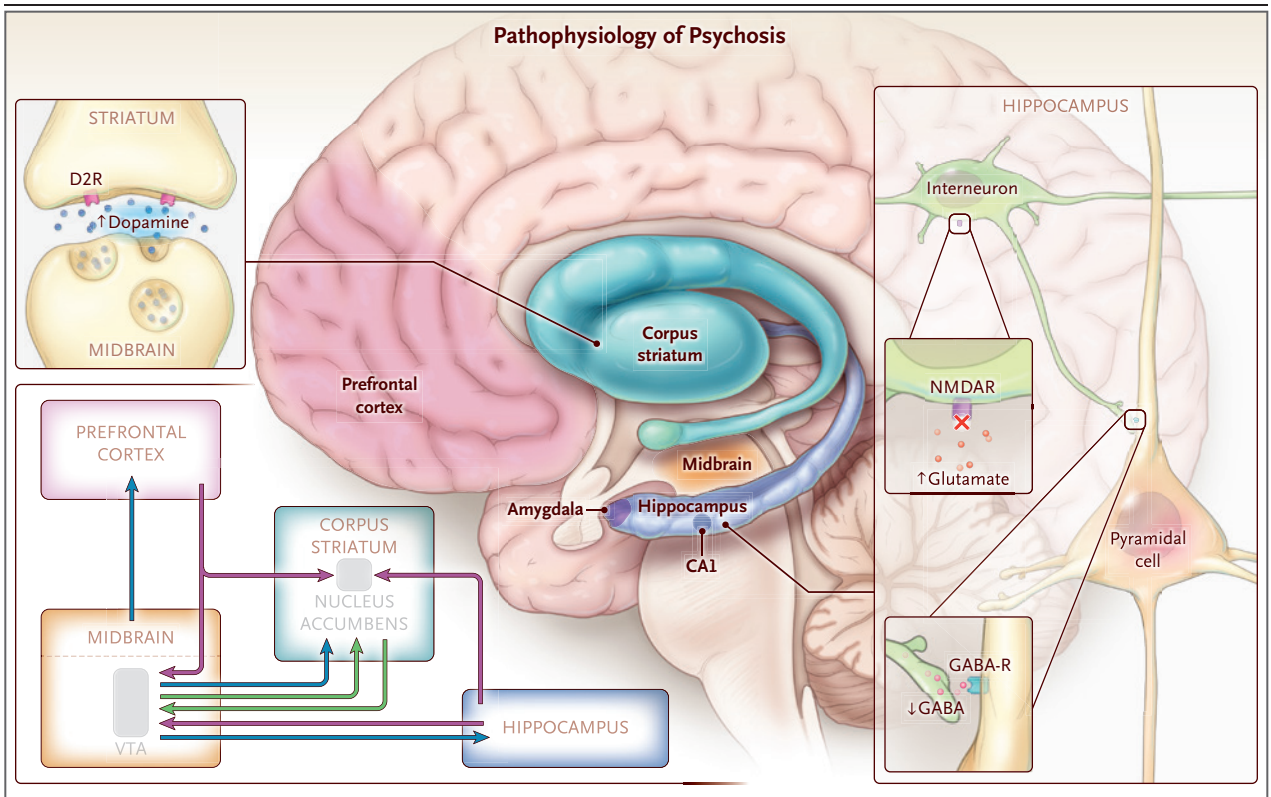

Figure 2. Pathophysiological Model of Psychotic Disorders.

A sagittal view of the brain through the midline depicts the hippocampus, midbrain, corpus striatum, and prefrontal cortex, all regions that are implicated in psychotic symptoms and disorders. The affected neurotransmitters include dopamine (blue arrows), glutamate (purple arrows), and γ-aminobutyric acid (GABA) (green arrows). Idiopathic psychoses (e.g., schizophrenia and mood disorders with psychotic symptoms) are believed to arise from overactivity of neurons that release glutamate onto cells located in and projecting from the CA1 region of the hippocampus. Deficits in hippocampal GABAergic interneurons and hypofunctioning *N*-methyl-D-aspartate glutamate receptors (NMDARs) (the red X denotes hypofunction) are the main molecules that are thought to be responsible for these disturbances. Shown in the hippocampus is a glutamate-expressing pyramidal cell and a GABA interneuron. Despite the increase in synaptic glutamate, there is underactivation of the interneuron. Also shown is the interneuron axon forming a synapse with the apical dendrite of the pyramidal cell. Because of understimulation, the interneuron releases less GABA, which in turn disinhibits the pyramidal cell and causes it to release more glutamate from hippocampal projections to the midbrain (ventral tegmental area [VTA]) and the corpus striatum (nucleus accumbens). Hippocampal overactivity augments dopamine release in the striatum either directly (at the level of the nucleus accumbens) or by stimulation of midbrain dopamine neurons, which project to the nucleus accumbens and the prefrontal cortex. Dopamine neurons in the midbrain further promulgate the dysregulation of dopamine and glutamate through a projection back to the hippocampus. Psychotic symptoms can be induced in nonidiopathic disorders that affect these pathways at various locations. For example, in autoimmune or toxic psychoses (e.g., psychoses due to PCP), the exogenous drug or antibody acts as an NMDAR antagonist, thus mimicking a constitutionally hypofunctioning NMDAR. In Alzheimer's disease, the cholinergic system is compromised and cholinergic inhibitory inputs to glutamateric cells in the hippocampus and dopaminergic cells in the midbrain are diminished. D2R denotes D2 receptor.

exert effects independently, or produce phenocopies of psychotic disorders.

AUTOIMMUNE AND INFLAMMATORY DISORDERS WITH PSYCHOSES

A special category of psychoses consists of those that develop with autoimmune and inflammatory disorders, in which autoantibodies stimulate or block neurotransmitter function in the brain, particularly the glutamate system. Interest in this group of disorders is both clinical, since the antibodies can be assayed and certain clinical syndromes identified, and biologic, in that these disorders may reveal mechanisms of psychosis.

Systemic Autoimmune Disorders and Psychosis

Psychotic symptoms occur in association with autoimmune diseases that have nervous system manifestations, especially SLE. Approximately 30% of persons with SLE have antibodies directed against double-stranded DNA that cross-react with epitopes of the glutamate NR2 subunit, a component of NMDAR.[23-25] Psychotic symptoms develop in some of these persons.

Paraneoplastic and Nonparaneoplastic Autoimmune Syndromes with Psychosis

Psychotic symptoms similar to those in schizophrenia are a central feature of certain forms of immune encephalitis (i.e., encephalitis due to antibodies directed against the glutamate NR1 subunit of NMDAR).[26] These antibodies and a psychotic syndrome occur mainly with ovarian teratomas, which are known to express dermoid-tissue epitopes that cross-react with neuronal markers. Normally, the brain is immunoprivileged, preventing antibody access to receptors on neurons. However, NMDAR expression on ectopic cells within dermoid tissue sensitizes the adaptive immune system to produce antibodies to NMDAR that are able to cross the blood–brain barrier to produce symptoms. Other autoantibodies (e.g., anti–metabotropic glutamate receptor 5 antibody) have putatively caused psychosis, but none are as well established as the NMDAR type.

DIAGNOSIS

Despite various etiologic and physiological hypotheses, the diagnosis of psychotic disorders is clinical and therefore based predominantly on the patient's history, observed behavior, and subjective reports, as well as results of the mental status examination (Table 1). Diagnostic tests, including neuroimaging and electroencephalographic (EEG), genotypic, toxicologic, and serologic assessments, are usually performed only in selected patients presenting with a first episode of psychosis or with psychotic symptoms associated with preexisting neurodegenerative diseases, other medical conditions, or substance abuse. Although some of these diagnostic tests reveal differences between psychotic patients and those without mental disorders, none have been shown to be sufficiently sensitive or specific to reliably diagnose individual cases of psychosis. They nevertheless expose biologic principles in the pathophysiology of psychosis.

NEUROIMAGING

Magnetic resonance imaging (MRI) and positron-emission tomography (PET) have revealed various abnormalities in patients with psychotic disorders. For example, patients with schizophrenia, schizoaffective disorder, or bipolar disorder with psychosis have focal volume reductions in the temporal, frontal, and parietal lobes and reduced cortical thickness in these and other brain regions.[27] In patients with schizophrenia, PET studies show increased synaptic dopamine levels in the ventral striatum and decreased levels in the frontal cortex,[28] and magnetic resonance spectroscopy shows increased glutamate levels in the prefrontal and medial temporal regions.[29,30] However, as with other putative biomarkers for psychotic disorders, these imaging findings differentiate groups of affected patients from healthy persons but are not sufficiently sensitive or specific for reliable diagnosis in individual patients and are therefore not used clinically.

NEUROPHYSIOLOGICAL TESTS

EEG assessment may be performed when psychotic symptoms first appear in patients for whom there are reasons to suspect a seizure disorder, a causative medical condition, neurodegenerative disease, or substance abuse. Specialized brain potentials that require computerized techniques to extract the signal from background EEG activity, such as potentials elicited by a variety of sensory, motor, and cognitive events ("event-related potentials"), have been found to be abnormal in patients with psychotic disorders. These tests show differences between groups of unaffected and affected persons and offer insights into the abnormal physiology in these disorders, but they are not sufficiently sensitive or specific to use clinically.

SEROLOGIC TESTS

Although the risk of tertiary syphilis of the brain, traditionally called "general paresis of the insane," is low in developed countries, serologic screening for syphilis is nevertheless recommended in the evaluation of a first episode of psychosis. In addition, immunologic conditions should be considered in cases of a sudden onset of psychotic symptoms associated with or follow-

ing a systemic viral infection or occurring at an age that is outside the typical age range for the onset of the idiopathic psychotic disorders. The diagnosis of these conditions is based mainly on the presence of IgG antibodies against the NR1 subunit of NMDAR in samples of blood or cerebrospinal fluid.

TREATMENT

PHARMACOLOGIC TREATMENT

Approximately 20 antipsychotic medications are currently marketed in the United States,[31] all of which work largely by blocking or mitigating the activity of dopamine at D2 receptors.[32] These medications are effective in treating psychotic symptoms in patients with various disorders, although their effectiveness depends on their safety profile, which varies with the drug's pharmacology and the nature of the underlying cause of the condition (e.g., dementia vs. drug-induced psychosis). The older — typical, or first-generation — medications have a propensity to cause extrapyramidal neurologic side effects, whereas the atypical, or second-generation, drugs are more likely to induce weight gain and disturbances in glucose and lipid metabolism.[32] An exception is clozapine, which produces few extrapyramidal effects and has therapeutic efficacy in patients with a partial response or no response to other antipsychotic agents.[32] However, clozapine can be associated with serious side effects, including seizures (in approximately 4% of patients), myocarditis (in 1%), and agranulocytosis (in 0.8%), and is therefore indicated mainly for the treatment of refractory psychotic symptoms.

Most patients with psychotic disorders are treated with short-acting oral or injectable agents requiring daily administration, but long-acting, injectable formulations of haloperidol, fluphenazine, olanzapine, paliperidone, and aripiprazole are available and useful for facilitating adherence to the treatment regimen, although the evidence for superior clinical effectiveness has been inconsistent.[33,34] Numerous agents have been examined as adjunctive treatments to antipsychotic medications, but their effects are modest, and evidence for their efficacy is limited.[35] The same is true for combinations of conventional antipsychotic drugs.

Drugs that have little or no D2-receptor affinity but do have predominant 5-HT_{2A} receptor antagonist effects (e.g., pimavanserin) may be useful for psychotic symptoms that are specifically due to dopamine-replacement treatment in patients with Parkinson's disease, for whom most antipsychotic drugs are relatively contraindicated because they may worsen parkinsonian symptoms. These 5-HT_{2A} receptor antagonists are being tested for psychotic symptoms in patients with dementia (ClinicalTrials.gov numbers, NCT03325556, NCT02035553, and NCT03118947). However, they have been less effective than conventional D2 receptor antagonists in the treatment of schizophrenia, schizoaffective disorder, and mood disorders with psychotic symptoms.[32] When psychotic symptoms are due to medical conditions, treatment should address the effects of the underlying disorder, including fever, infection, electrolyte and calcium imbalances, and endocrine disturbances, before antipsychotic drugs are considered. A careful review of the patient's medications, particularly those with anticholinergic activity, will expose the cause of transient delirious and psychotic behavior in many instances.

NEUROMODULATION

Brain-stimulation techniques, such as electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), transcranial direct-current stimulation (tDCS), and deep-brain stimulation (DBS), have been used for psychotic symptoms in specific disorders. ECT is effective for catatonia and for mood disorders with psychotic symptoms and is indicated in patients with schizophrenia or schizoaffective disorders when symptoms are unresponsive to antipsychotic medications.

One promising application of neuromodulation is for control of psychotic auditory or verbal hallucinations. Initial studies were performed with TMS applied over the region of the left temporal lobe that overlies the auditory cortex.[36] More recently, tDCS applied over the region of the auditory cortex has led to reductions in hallucinations and in persistent negative symptoms of schizophrenia, such as apathy and social withdrawal.[37]

DBS, the most invasive of the neuromodulation techniques, has been used for psychotic states when all other treatments have failed. The procedure entails surgically implanting an electrode into target brain regions and stimulating

them with high-frequency electrical pulses. At present, DBS is approved by the Food and Drug Administration for the treatment of Parkinson's disease and refractory obsessive–compulsive disorder,[38] and potential applications for the treatment of refractory depression and idiopathic psychotic disorders are being examined.

PSYCHOSOCIAL APPROACHES TO TREATMENT

Cognitive and behavioral rehabilitation has been used in the treatment of idiopathic psychotic disorders — in particular, schizophrenia.[39] The most widely studied of these techniques is social skills training, in which patients are instructed, after stabilization of their acute psychotic symptoms, about appropriate modes of behavior and communication with others and about practical life skills that may have been impaired by psychotic disorders. Another psychosocial treatment with strong empirical support is family psychoeducation, which enables family members to help support the patient's recovery.

Cognitive behavioral therapy (CBT), a treatment originally developed for mood and anxiety disorders, may also be useful for psychotic symptoms. Specific CBT approaches used in treating patients with schizophrenia include cognitive restructuring (i.e., engaging patients to change beliefs about their hallucinations and delusions), behavioral exposure to stimuli that trigger psychotic symptoms to enhance reality testing, self-monitoring, and graded coping skills. CBT in patients with schizophrenia can also help to reduce the distress caused by hallucinations or delusional beliefs.

FUTURE DIRECTIONS

EARLY INTERVENTION AND PREVENTION

Current pharmacologic treatments for psychotic disorders, which act on D2 receptors to inhibit dopamine neurotransmission, are considered to be symptom-suppressing rather than disease-modifying. However, in patients with idiopathic psychotic disorders who are in the early stages of illness, treatment at the first episode of schizophrenia or schizoaffective disorder shortens the duration of psychotic episodes, reduces recurrences, and limits progressive decline in intellectual and functional capacity over the course of the patient's life (Fig. 1). On the basis of these observations, a structured service model for first episodes of psychosis, Coordinated Specialty Care, has been developed to improve the clinical benefits of treatment.[1,40,41] This model of care includes pharmacotherapy, psychosocial therapies (including those for substance abuse), and public outreach to promote identification of and reduction in the duration of untreated psychotic symptoms.[42]

Enthusiasm for early intervention in and prevention of idiopathic psychotic disorders has led investigators and the National Institute of Mental Health to determine how to extend this approach to patients in the prodromal stage of illness in order to prevent the onset of a more disturbing psychotic disorder. Before this approach can be applied, better diagnostic methods must be developed, because the current criteria for identifying persons with attenuated psychotic symptoms who are believed to have a high clinical risk of conversion to a syndromal form of psychosis have a false positive rate that is higher than 50%. Consequently, a diagnostic test is needed that can identify psychotic episodes that will progress to a syndromal psychosis, as well as episodes that are stable or transient and those that can be attenuated. Treatments so far have been shown to be effective for alleviation of symptoms but not for prevention of conversion to syndromal psychosis.[43]

INNOVATIVE TREATMENTS FOR IDIOPATHIC PSYCHOTIC DISORDERS

It has been hoped that precision medicine will provide new targets such as the products of newly identified genes associated with psychotic disorders. In this context, a strategy that has been used entails exome sequencing of large cohorts of patients in the hope of identifying rare mutations for which compounds acting on the gene pathway can be sought.

SUMMARY

Psychosis consists of a constellation of symptoms reflecting gross disturbances in cognitive and perceptual functions that are mediated, in most cases, by the dysregulation of dopamine and glutamate neurotransmission. Dopamine D2 receptor antagonists are the mainstay of pharmacologic treatment for idiopathic psychotic dis-

orders and for psychotic symptoms associated with neurodegenerative diseases but are not consistently useful for psychotic symptoms caused by other medical conditions or drug toxicity. Despite extensive research, few mechanistic innovations in the pharmacologic treatment of psychotic symptoms have been achieved. Neuromodulation (through DBS, TMS, and tDCS) and early detection and intervention strategies using D2 receptor antagonists in the context of Coordinated Specialty Care for schizophrenia and schizoaffective disorder may lead to symptom reduction and disease-modifying treatment.

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